

The mother liquor, on remaining overnight, gave a small quantity of needles which, after two crystallizations from hexane, melted at 148°. This was shown by a mixed m.p. to be identical with "urethan C" above.

Seven crystallizations from hexane of the first solid isolated (78–80°) raised its m.p. to 91°; a mixed m.p. with the phenylurethan derivative of 1-(*o*-hydroxyphenyl)-2-(*p*-chlorophenyl)-propane (V) (m.p. 91.5–92°, "urethan B") gave no depression.

The treatment of 1-(*o*-hydroxyphenyl)-2-(*p*-chlorophenyl)-propane (V) (680 mg.) with aluminum bromide and chlorobenzene employing the same mole ratios and isolation procedure as given above, resulted in the recovery of 560 mg. (82%) of starting material, identified as the phenylurethan.

The Initial Reaction between *o*-Allylphenol and Aluminum Bromide in Chlorobenzene.—To a solution of 13.4 g.

of *o*-allylphenol in 500 cc. of chlorobenzene was added a solution of 59.4 g. of aluminum bromide in 500 cc. of chlorobenzene. Immediately after mixing the two solutions, 300 cc. of water was added to quench the reaction. Hexane (300 cc.) was added to facilitate the removal of the water layer and the organic layer was extracted three times with 100-cc. portions of 20% aqueous sodium hydroxide followed by three extractions with 100-cc. portions of Claisen alkali.

The combined Claisen alkali extracts were acidified with hydrochloric acid, extracted three times with 200-cc. portions of ether and dried. Removal of the ether gave a viscous red oil which, when distilled, gave 10.5 g. (50%) of II as a light yellow oil, b.p. 180–185° (2 mm.), n_D^{25} 1.5869.

The phenylurethan of this material was identical in all respects with "urethan A."

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

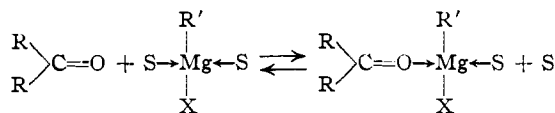
Solvent Effects in the Grignard Reaction¹

BY RICHARD N. LEWIS² AND JAMES R. WRIGHT

The effect of the basicity of the solvent on the course of the Grignard reaction has been investigated. A strongly basic solvent (pyridine) retards the reaction between a Grignard reagent and a ketone, while a weakly basic solvent (anisole, phenetole) permits a rapid reaction. A solvent of intermediate basicity (tetrahydrofuran) results in abnormal products. It appears that a basic solvent retards the formation of the ketone-Grignard coordination compound which is an intermediate in both normal and abnormal reactions. It also retards the second step in the normal reaction. Both steps require the displacement of a solvent molecule from the Grignard reagent. Reactions studied include one in which steric hindrance is small (benzophenone-ethylmagnesium bromide) and four in which it is large. Yields of normal products were uniformly higher in anisole than in ether.

The effect of solvents in the Grignard reaction should be discussed in the light of the mechanism of the reaction. When a Grignard reagent reacts with a ketone the first step appears to be the formation of a coordination compound, in which one of the coordination points of the magnesium is taken up by the carbonyl oxygen. Pfeiffer and Blank³ have actually isolated such compounds as solids or oily liquids which separated from ether solution; treatment with water regenerated the ketone.

It is unlikely for steric reasons that the magnesium atom in these compounds could coordinate more than two molecules of solvent or ketone. Thus, when a Grignard reagent coordinates with a ketone, there must be a simultaneous displacement of a solvent molecule, possibly in a manner similar to nucleophilic displacement on a carbon atom. The extent of ketone coordination at equilibrium will depend on the relative nucleophilic character of ketone and solvent. This step may be represented by the following equation, where S is a solvent molecule.⁴

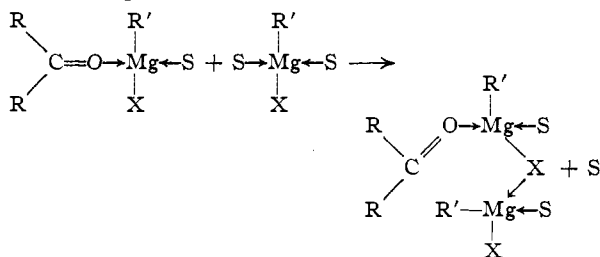


The coordinating power of a solvent for a light atom like magnesium is, in general, a function of the base strength of the solvent. In comparison with ether, a strongly basic solvent, which forms a

strong bond with the metal, should retard the Grignard reaction by retarding the formation of the ketone-complex. A feebly basic solvent, on the other hand, should facilitate the reaction.

The second step in the reaction appears not to take place through an internal rearrangement of the addition compound but through the approach of a second molecule of Grignard reagent. Thus, Pfeiffer and Blank obtained no tertiary alcohol from benzophenone and ethylmagnesium bromide in the absence of excess Grignard reagent. An interesting cyclic intermediate involving two molecules of the Grignard reagent has been proposed by Swain and Boyles,⁵ on the basis of the favorable effect of magnesium bromide in the reaction of propylmagnesium bromide with diisopropyl ketone. Magnesium bromide, because of its stronger coordinating power, displaces the Grignard reagent in the first addition compound, and is more effective than the Grignard reagent in polarizing the carbon-oxygen double bond.

The formation of such a cyclic intermediate again requires the displacement of a solvent molecule, and is therefore affected by the basicity of the solvent in the same way as the first step. The second step can be formulated as



(5) C. G. Swain and H. B. Boyles, *THIS JOURNAL*, **73**, 870 (1951).

(1) From the Ph.D. thesis of James R. Wright, June, 1951. Presented at the Southwest Regional Meeting, A.C.S., Austin, Texas, October, 1951.

(2) Olin Industries, New Haven, Conn.

(3) P. Pfeiffer and H. Blank, *J. prakt. Chem.*, **163**, 242 (1939).

(4) J. R. Johnson in "Organic Chemistry," 2nd ed., edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1880.

The ring structure is the same as that given by Swain and Boyles, except that we have placed a halogen atom instead of a carbon atom between the magnesium atoms.

The role of the solvent will be particularly important where competing "abnormal" reactions are possible, since any hindrance to the normal reaction will favor the formation of abnormal products.

Although many solvents have been used for the Grignard reaction, the influence of solvent basicity has never been the subject of a systematic study. However, a few scattered observations lend support to the theory presented here. Gilman and Jones,⁶ for instance, report that malachite green can be prepared by reaction between phenylmagnesium bromide and Michler ketone in benzene, but not in ether. Sachs and Sachs⁷ state that phenylmagnesium bromide does not react with Michler ketone in quinoline; they attribute this inertness to the stability of the Grignard-quinoline complex. In the reaction of methylmagnesium iodide with acetophenone the extent of enolization, an abnormal reaction, increased from 3% in xylene and 12% in isoamyl ether to 78% in dioxane or pyridine.⁸ Kharasch and Weinhouse⁹ have found that replacement of ether by benzene or pyridine in the reaction between benzophenone and butylmagnesium bromide results in higher yields of the reduction product, benzhydrol.

The solvents selected for the present study, in estimated decreasing order of base strength, were: pyridine, tetrahydrofuran, ether, dioxane, phenetole, anisole and benzene. The order among the ethers is assumed to be the same as that in the analogous amines, whose basic ionization constants at 25° are: pyrrolidine,¹⁰ 1.30×10^{-3} ; diethylamine,¹¹ 9.6×10^{-4} ; morpholine,¹² 2.44×10^{-6} ; N-ethylaniline,¹¹ 1.29×10^{-9} ; N-methylaniline,¹¹ 7.1×10^{-10} . Steric hindrance to compound formation may change the order considerably, as Brown¹³ has shown in the case of addition compounds of trimethylboron with bases. The base strength of ethers toward boron trifluoride has been shown to decrease in the order, tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether.¹⁴ The difference between diethyl ether and tetrahydrofuran is that the latter has its loose ends tied back where they cannot interfere with the boron. Dimethyl ether, of course, has no loose ends. The steric effect should cause ethyl ethers in general to be less basic than methyl ethers, except in proton addition.

Most of our work was done with the ethylmagnesium bromide-benzophenone reaction. Benzophenone was chosen because it does not undergo enolization, which is one of the side reactions of aliphatic ketones. Also, it was hoped

that all the products would be easily separated solids.

Ethylmagnesium bromide was the most suitable Grignard reagent for this study, since preliminary experiments indicated that methyl- and phenylmagnesium bromides would give good yields of tertiary alcohols, even under unfavorable conditions, and it seemed unlikely that they would show any pronounced solvent effect. On the other hand Kharasch and Weinhouse⁹ have shown that Grignard reagents with alkyl groups larger than ethyl are likely to reduce benzophenone to benzhydrol.

Grignard reactions in general, and this one in particular, are unusually sensitive to reaction conditions, even where the solvent is not changed. In order to minimize benzopinacol formation, which can be caused by metallic magnesium,^{9,15} or by iodine,¹⁶ the Grignard solutions were always filtered before use, and no iodine or other catalysts were used. In the majority of cases the Grignard reagent was prepared in the solvent to be studied. Sometimes, however, the reagent was prepared in ether, which was later removed and replaced with the desired solvent. Several experiments were conducted in which ratio of reagents, order of addition, and reaction temperature were varied. In the procedure finally adopted the Grignard solution or suspension was cooled in an ice-bath; an equimolecular quantity of the ketone was dissolved in the solvent and run in over a period of one hour; the mixture was allowed one hour to warm up to room temperature, then hydrolyzed with saturated ammonium chloride solution; and the products were separated and identified.

It was of interest to extend the study of solvent effects to other Grignard reactions, particularly to those in which steric hindrance is likely to lead to low yields and abnormal products. Four such reactions chosen for this investigation were: *t*-butylmagnesium chloride and acetaldehyde, *t*-butylmagnesium chloride and acetone, *n*-propylmagnesium bromide and diisopropyl ketone, 3-methyl-3-hexylmagnesium bromide and acetaldehyde.

Experimental

Filtering Apparatus.—Solutions of the Grignard reagent were forced by low nitrogen pressure up through a 9-mm. tube loosely packed with glass wool, into the filtering chamber, having at the bottom a one-inch sintered glass disk (Ace Glass, Inc., porosity D) and at the top a stopcock to release trapped gases. The filtrate, still under nitrogen, was collected in a graduated funnel.

Magnesium.—Two separate lots of magnesium "for Grignard's Reaction" (Baker and Adamson, code 1904) were used. Upon a request for analysis we were informed that four separate lots were found to contain 0.002% Fe, less than 0.001% Ni, less than 0.002% Co. Qualitative analysis failed to reveal any of these elements in our lots. Nevertheless an impurity must have been present, as the older lot, used in all runs through 16, gave consistently gray-brown solutions, while the second lot, used in subsequent runs, produced almost colorless solutions.

Reactions of Grignard Reagents with Benzophenone in Ether.—Six condensations between ethylmagnesium bromide and benzophenone in ether are included in Table I. The filtered Grignard reagents, prepared in the absence of catalysts, were analyzed by acid titration of aliquots.¹⁷

(15) C. R. Noller, *ibid.*, **53**, 635 (1931).

(16) H. Gilman and R. E. Pothergill, *ibid.*, **51**, 3149 (1929).

(17) H. Gilman, P. D. Wilkinson, W. P. Fishel and C. H. Meyers, *ibid.*, **45**, 150 (1923).

(6) H. Gilman and R. G. Jones, *THIS JOURNAL*, **62**, 1243 (1940).

(7) F. Sachs and L. Sachs, *Ber.*, **37**, 3088 (1904).

(8) M. Lief, G. F. Wright and H. Hibbert, *THIS JOURNAL*, **61**, 865 (1939).

(9) M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

(10) L. C. Craig and R. M. Hixon, *THIS JOURNAL*, **53**, 4367 (1931).

(11) N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3469 (1932).

(12) A. R. Ingram and W. F. Luder, *ibid.*, **64**, 3043 (1942).

(13) H. C. Brown, H. I. Schlesinger and S. Z. Cardon, *ibid.*, **64**, 325 (1942); also later papers.

(14) H. C. Brown and R. M. Adams, *ibid.*, **64**, 2557 (1942).

Concentrations of Grignard reagent and ketone were approximately one molar before mixing. Factors varied were: order of addition, ratio of reactants, heating period. In runs without a heating period the ketone and Grignard were mixed in one hour at 0°, given one hour to warm to room temperature and hydrolyzed. Other runs included a five-hour reflux period. Except in cases where excess Grignard reagent was used, Gilman's color test¹⁸ was always negative at the end of a run, possibly because the Michler ketone fails to react in the presence of the more reactive benzophenone.¹⁹

In addition to unreacted benzophenone, m.p. 48°, and ethyldiphenylcarbinol, m.p. 92–94°,²⁰ there were sometimes found 1,1-diphenylpropene, m.p. 51–52°,²¹ benzhydrol, m.p. 68°, and benzopinacol, m.p. 186°. Separation of the various products was accomplished by fractional crystallization. Recovered benzophenone could generally be removed by dissolving it in petroleum ether. The others had solubilities in decreasing order of their melting points in methanol, ethanol, acetic acid, carbon tetrachloride and ligroin. Benzopinacol and ethyldiphenylcarbinol were separated with some difficulty¹⁸ by crystallization from acetic acid.

In most runs the recovery of benzophenone and its derivatives was over 90%, much of the loss occurring in the crystallization process. It is possible that even when only two compounds were isolated small amounts of the others were present.

Methylmagnesium bromide and phenylmagnesium bromide gave good yields of methyldiphenylcarbinol, m.p. 80–81°, and triphenylcarbinol, m.p. 160–161°, and there was no difficulty in isolating them. The products from propylmagnesium bromide were not completely analyzed, but both benzhydrol and benzopinacol were identified.

Ethylmagnesium Bromide in Other Solvents.—In a typical experiment (run 9) the Grignard reagent was prepared in ether and filtered as before. A measured amount of solution, containing 0.15 mole was run into the reaction flask. It was then evaporated to complete dryness by heating on the steam-bath and evacuating to 15 mm. for one hour. Four hundred cc. of benzene was added and the mixture was heated again until the benzene began to distil. The solid residue did not dissolve, but stirring reduced it to a fine suspension. To this suspension, cooled in ice, was added in 1.5 hours 27.4 g. of benzophenone in 250 cc. of benzene. A momentary red color appeared with the addition of each drop. Then the mixture was refluxed at 80° for five hours. It was then hydrolyzed and the benzene was removed by distillation.

In another run only 150 cc. of benzene was used. To prevent caking of the residue it was added before all the ether was evaporated. The rest of the ether was removed by heating until the benzene began to distil (run 10).

In two runs with anisole the Grignard reagent, prepared in ether, was evaporated to dryness before adding the anisole. In one of these (run 9) the reaction mixture was heated five hours at 35° to simulate the conditions in boiling ether. In run 7 the mixture was hydrolyzed immediately after coming to room temperature.

In run 20 the ethylmagnesium bromide was prepared in anisole directly. The usual procedure was followed, except that the reaction had to be started by local heat from a small flame. The ethyl bromide in anisole was added in 1.5 hours without cooling, and the mixture was heated an additional 1.5 hours at 85°. The yield of Grignard reagent was 53%. No filtration was attempted in this case because of the viscosity of the solution.

In phenetole (run 25) difficulty was encountered in starting the reaction between ethyl bromide and magnesium, until 3 cc. of ethylmagnesium bromide in ether was added. After the addition of 32.7 g. (0.3 mole) of ethyl bromide and 200 cc. of phenetole the mixture was heated 1.5 hours at 85°, then allowed to settle for two hours. The solution was filtered with nitrogen pressure through a 10-mm. tube filled with glass wool. The yield of Grignard reagent was 67.6%. A portion of this solution (135 cc., 0.15 mole) was cooled in ice and 27.4 g. (0.15 mole) of benzophenone in 100 cc. of phenetole was added in 45 minutes. A brown color

developed at first; later it turned pink and the pink color remained until 15 minutes after the addition. Stirring was continued for another 1.5 hours before hydrolysis.

For the runs in pyridine, tetrahydrofuran and dioxane the Grignard reagent was prepared in ether and evaporated to complete dryness as in run 9. On addition of pyridine to the still warm residue a rapid distillation of ether was observed, and the solid dissolved completely. Tetrahydrofuran had a somewhat similar effect, but the evolution of ether was not so rapid. With dioxane there was no visible evolution of ether, and only part of the solid dissolved. In each case benzophenone in the same solvent was added to the cooled Grignard reagent, and the mixture was brought to room temperature and hydrolyzed. Separation from water and salts was accomplished by extraction with ether. The results are shown in Table I. No crystals could be obtained from the dioxane run. The oily residue distilled at 144–149° at 2 mm. pressure. This is 20° higher than the calculated boiling point of benzophenone, and may indicate a mixture of alcohols, but not benzopinacol.

Preparation of Methyl-*t*-butylcarbinol.—*t*-Butylmagnesium chloride was prepared in ether in 2.5 hours without cooling.²² The yield, after filtration, was 64%. To the cooled solution (261 cc. containing 0.605 mole) was added in 1.25 hours 26.6 g. (0.605 mole) of acetaldehyde in 100 cc. of ether. After hydrolysis, drying, and distillation through an efficient, glass-packed column, 25.4 g. of methyl-*t*-butylcarbinol (pinacolyl alcohol) was obtained (42%); b.p. 120.5–122°, n_D^{25} 1.4148. Reported constants²³ are: b.p. 120.4°; n_D^{20} 1.4148.

An attempt to prepare *t*-butylmagnesium chloride in anisole directly was unsuccessful. To make an anisole solution, the Grignard reagent (0.905 mole) was prepared in ether, evaporated to dryness at 40° and 20 mm., dissolved in 150 cc. of anisole, and heated at 20 mm. until anisole began to distil. The solution was cooled in ice and treated as before. The yield of carbinol was 48 g., 53.5%; b.p. 120–121°, n_D^{20} 1.4155.

Preparation of Dimethyl-*t*-butylcarbinol.—*t*-Butylmagnesium chloride in ether (400 cc., 0.564 mole) was cooled in ice, and 32.8 g. (0.564 mole) of acetone (Eastman Kodak Co. white label) in 100 cc. of ether was added in one hour. Each drop added produced a slight yellow color. After standing one hour the mixture was again cooled to 0° and hydrolyzed with saturated ammonium chloride solution. The ether layer was dried, mixed with 50 cc. of anisole as a booster, and distilled. A 4.3-g. fraction came over at 130–132°, n_D^{25} 1.4275, representing a 6.6% yield of the carbinol. The reported b.p. is 128–130°.²⁴ No refractive index has been reported.

A solution in anisole was prepared from an ether solution of 0.625 mole of *t*-butylmagnesium chloride. To the cold solution was added 36.2 g. (0.625 mole) of acetone in 100 cc. of anisole in 1.5 hours. The yield of carbinol, b.p. 130–132°, n_D^{25} 1.4281, worked up as in the last run, was 17.8 g., 15.4%.

Preparation of *n*-Propyldiisopropylcarbinol.—*n*-Propylmagnesium bromide was prepared in 300 cc. of anisole from 36.5 g. (1.5 mole) of magnesium and 184.5 g. (1.5 mole) of *n*-propyl bromide. Reaction started in 20 minutes with a little heating, and the alkyl halide was added over a 2.25-hour period; yield 0.778 mole, 51.8%. To the cold solution was added in 1.5 hours 46.8 g. (0.408 mole) of diisopropyl ketone in 150 cc. of anisole. No visible reaction could be observed during the addition and the mixture was stirred an additional hour. A color test showed unreacted Grignard reagent. Hydrolysis produced a large amount of gas (propane). A fraction collected at 119–120° and 90 mm. weighed 30.1 g., a yield of 46.8%. Index of refraction, n_D^{25} , was 1.4409 compared with n_D^{25} 1.4401 previously reported.⁵

A discussion of the factors which affect the Grignard reaction requires an understanding of the mechanisms of the abnormal reactions as well as that of the normal one. It is now well established that reduction to a secondary alcohol proceeds by

(22) H. Gilman and E. A. Zoellner, *Rec. trav. chim.*, **47**, 1058 (1928).

(23) F. C. Whitmore and P. L. Meunier, *This Journal*, **55**, 3722 (1933).

(24) R. G. Huston and W. T. Barrett, *J. Org. Chem.*, **11**, 657 (1946).

(18) H. Gilman and F. Schulze, *This Journal* **47**, 2002 (1925).

(19) R. N. Lewis and J. R. Wright, *ibid.*, **74**, 1257 (1952).

(20) F. F. Blicke and L. D. Powers, *ibid.*, **51**, 3378 (1929).

(21) K. von Auwers, *Ber.*, **62**, 693 (1929).

TABLE I
 REACTION OF GRIGNARD REAGENTS, RMgBr, WITH BENZOPHENONE

Run ^a	R	Solvent	Ratio ^b	Reflux period, hours	Ph ₂ CO	Yield of products, %		Total
						Ph ₂ CR ₂ OH	Others	
1	Ethyl	Ether	1:1	5	80.1	..	11.5 V ^c	91.6
2	Ethyl	Ether	2:1	5	43	27.3	17.5 V ^c	87.8
3	Ethyl	Ether	2:1 ^d	5	..	24.2	61.2 IV ^c	85.4
15	Ethyl	Ether	1:1	None	19	38.3	9.9 V ^c	67.2
16	Ethyl	Ether	2:1 ^d	None	21.2	64.6	..	85.8
18 ^e	Ethyl	Ether	1:1	None	48.4	44.1	..	92.5
4	Phenyl	Ether	2:1	5	13	78	..	91
5	Phenyl	Ether	1:1 ^d	5	6.7	87.5	..	94.2
6	Methyl	Ether	1:1 ^d	5	11	85	..	96
7	Methyl	Ether	1:1	5	10.6	81.5	..	92.1
8	Propyl	Ether	1:1	5	?	?	2.0 V ^c , ^g	?
9	Ethyl	Benzene ^f	1:1	5 ^g	Trace	Trace	Mostly IV ^c	?
10	Ethyl	Benzene ^f	1:1	None	63.9	28	..	91.9
12	Ethyl	Pyridine	1:1	None	95.7	95.7
13	Ethyl	Tetrahydrofuran	1:1	None	55.6	..	29.7 III, ^c 5.8 V ^c	91.1
14	Ethyl	Dioxane	1:1	None	Oil	?
11	Ethyl	Anisole ^f	1:1	None	39	48.8	..	87.8
17 ^e	Ethyl	Anisole ^f	1:1	None	41.2	53.7	..	94.9
19 ^e	Ethyl	Anisole ^f	1:1	5 ^h	39.8	32.8	..	72.6
20 ^e	Ethyl	Anisole	1:1	5 ^h	13.2	80.5	..	93.7
21 ^e	Ethyl	Phenetole	1:1	None	5.5	84.8	..	90.3

^a Runs 17 through 21 were made with the newer magnesium. ^b Ratio of Grignard reagent to ketone. ^c III is benzhydrol, IV is diphenylpropene, V is benzopinacol. ^d Inverse addition. ^e Benzhydrol was also identified. ^f Solvated ether may also have been present. ^g At 80°. ^h Five hours at 35°.

TABLE II

SOLVENT EFFECT IN STERICALLY HINDERED REACTIONS^a

Grignard reagent	Carbonyl compound	Solvent	Ratio	Carbinol yield, %
<i>t</i> -BuMgCl	MeCHO	Ether	1:1	42.0 ^b
<i>t</i> -BuMgCl	MeCHO	Anisole	1:1	53.5
<i>t</i> -BuMgCl	Me ₂ CO	Ether	1:1	6.6 ^c
<i>t</i> -BuMgCl	Me ₂ CO	Anisole	1:1	15.4
<i>n</i> -PrMgBr	<i>i</i> -Pr ₂ CO	Ether	2:1	29.0 ^d
<i>n</i> -PrMgBr	<i>i</i> -Pr ₂ CO	Anisole	1.9:1	46.8
R ₃ CMgBr ^e	MeCHO	Ether	1:1	16.0 ^f
R ₃ CMgBr ^e	MeCHO	Anisole	1:1	25.0 ^f

^a Normal addition, no heating period; new magnesium used. ^b A 52.1% yield based on *t*-butyl chloride has been reported in a 20-mole run, ref. 23. ^c G. Edgar, G. Calingaert and R. E. Marker, THIS JOURNAL, 51, 1483 (1929), report 28% from "very pure acetone." ^d Ref. 5. ^e *β*-Methyl-*β*-hexylmagnesium bromide. ^f Miss Susan Duck, worth of this Laboratory, who conducted these reactions—has kindly permitted us to include the results here.

an electronic rearrangement in a six-atom system present in the 1:1 addition compound.²⁵ 1,4-Addition²⁶ and enolization²⁷ proceed by similar rearrangements, except where the six-atom ring cannot exist.²⁸ These reactions are, in all probability, unimolecular, while the normal reaction is at least bimolecular, since it requires the approach of a second molecule of the Grignard reagent. It is hindrance in this step that produces abnormal products.

The influence of the solvent is clearly shown by a comparison of runs 10, 12, 13, 14, 17, 18, 20 and 21. In the most basic solvent, pyridine, the Grignard reagent is so strongly solvated that it is

incapable of any reaction with the ketone, at least under the mild conditions employed. In tetrahydrofuran a considerable amount of reaction took place, but the only products were benzopinacol and an unexpectedly large amount of benzhydrol. While the solvent is basic enough to displace the ether, which is bound very tenaciously, the formation of benzhydrol shows that solvation was not strong enough to prevent the necessary ketone complex from forming. In ether ethyldiphenylcarbinol was the major product and there was no detectable amount of benzhydrol. Since both products proceed through the same intermediate, we attribute the difference in behavior of the solvents to a strong hindrance to the second step in tertiary alcohol formation in tetrahydrofuran. In ether the hindrance is less, because of weaker solvation, and the normal reaction predominates. Kharasch and Weinhouse⁹ reported only 2% benzhydrol from ethylmagnesium bromide in ether.

The runs in anisole show generally better yields of tertiary alcohol than those in ether, and no by-products were formed, except possibly in run 19, where the mixture was heated. The most striking improvement occurred when the Grignard reagent was prepared in anisole, run 20. The relatively low yield in run 17 could be the result either of residual ether attached to the magnesium atoms or of partial destruction of the Grignard reagent in the drying process.

Phenetole, on the basis of a single run, appears to be the best solvent for the normal reaction.

Benzene, theoretically the least basic solvent, proved to be unsatisfactory, possibly because the Grignard reagent is insoluble in it. Dioxane is probably about as basic as tetrahydrofuran, but the experiment is inconclusive,

(25) H. S. Mosher and E. LaCombe, THIS JOURNAL, 72, 3994 (1950).

(26) R. E. Lutz and W. G. Reveley, *ibid.*, 63, 3180 (1941).

(27) R. E. Lutz and C. J. Kibler, *ibid.*, 62, 360 (1940).

(28) E. R. Alexander and G. R. Coraor, *ibid.*, 73, 2721 (1951).

It is significant that in almost every case unreacted benzophenone could be recovered, even when an excess of the Grignard reagent was used. Although the unreacted Grignard could be detected¹⁸ only where it was in excess, it was undoubtedly present in every case. The failure of the color test can be attributed to the fact that the Grignard was tied up as the addition complex with benzophenone, and to the fact that the Michler ketone used in the test is even less reactive than benzophenone, the reaction rates being in the ratio of 0.313:1.¹⁹

The good yields obtained in anisole and phenetole can be explained by a faster, and therefore more complete, reaction. The reaction in ether can be speeded up with an excess of Grignard, as is evident from a comparison of runs 16 and 18. The yield has been increased to 80% by allowing a 4:1 excess of ethylmagnesium bromide to stand for 24 hours at 0° with benzophenone.²⁰ The fact that the order of mixing had little effect on the yield is further evidence of a slow reaction.

Increasing the reaction temperature, contrary to expectation, decreased the yields in each of the following pairs: 1 and 15, 3 and 16, 9 and 10, 17 and 19. The inference here is that the magnesium alcoholate produced is decomposed by heating. Perhaps even room temperature is too high.

In reactions subject to a good deal of steric hindrance the use of anisole as a solvent has resulted in a marked increase in yield (Table II). In these

reactions it is probable that anisole not only increases the reaction rate, but decreases the proportion of by-products.

Two unexpected products, benzopinacol and 1,1-diphenylpropene, have been isolated from ethylmagnesium bromide and benzophenone. The benzopinacol seems to be due to some unidentified impurity in one lot of magnesium, and is associated with dark-colored Grignard solutions. Kharasch and Sayles²¹ have observed such coupling reactions in the presence of manganous, ferric, cobaltous or cuprous chlorides. It is possible that our magnesium contained one of these metals. Benzopinacol was not found when the Grignard reagent was added to the ketone (inverse addition). Diphenylpropene, the dehydration product of ethyl-diphenylcarbinol, seems to result from heating the reaction mixture. It was previously observed by Kharasch and Sayles, and probably constitutes the unidentified material observed by Pfeiffer and Blank.³

The factors which seem to have the most effect in producing good yields are: an excess of Grignard reagent,³ a stoichiometric amount of magnesium bromide,⁵ a low temperature combined with a long reaction time,²⁰ a solvent of low basicity like anisole. It is to be hoped that the best yields will result from a combination of all of these factors.

(29) M. S. Kharasch and D. L. Sayles, *ibid.*, **64**, 2972 (1942).

NEWARK, DELAWARE

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Reactivity of Substituted Benzophenones in the Grignard Reaction¹

BY RICHARD N. LEWIS² AND JAMES R. WRIGHT

The relative reactivities of benzophenone and seven of its *p*-substitution products toward methylmagnesium iodide have been investigated. Relative rate constants were calculated from the relative amounts of carbinol and methane produced in competition experiments with α -naphthol. It was found that the reaction rate is increased by electron-withdrawing groups,

Hibbert,³ in 1912, devised a rapid method for the determination of the relative reactivities of ketones toward methylmagnesium iodide. The method is based on competition between the condensation of the Grignard reagent with the ketone and its reaction with α -naphthol to produce methane. If the Grignard reagent and α -naphthol are present in equal amounts an almost quantitative yield of methane is obtained; but if a carbonyl compound is added, part of the Grignard reagent is used up in the formation of an alcohol. The more reactive the ketone the less methane will be formed, provided that the ratio of ketone to naphthol and Grignard is constant.

The object of the present work was to establish the relative reactivity of a series of *p*-substituted benzophenones in the Grignard reaction, in order to learn something about the nature of the reaction. Hibbert's procedure was followed rather closely. In brief, the ketone and α -naphthol in a 4:1 mole

ratio⁴ were dissolved in phenetole, and an insufficient amount of methylmagnesium iodide in phenetole was added. The amount of methane produced is shown in Table I.

It is not possible to calculate rate constants from this work, but by making certain assumptions the ratios of rate constants can be determined. We assume that both ketone and naphthol react by second order reactions; then, letting (K), (N) and (G) represent concentrations of ketone, naphthol and Grignard, and the subscripts, o and f, the original and final concentrations

$$\begin{aligned} d(K)/dt &= k(K)(G); & d(N)/dt &= k_N(N)(G); \\ d(K)/d(N) &= k(K)/k_N(N); & \text{and} \\ \Delta(K) &= \int_{(K)_f}^{(K)_o} d(K) \doteq \int_{(N)_f}^{(N)_o} \frac{k(K)d(N)}{k_N(N)} \end{aligned}$$

Now the change in (K) is proportionately much smaller than the change in (N) and is never more than 18%. For the purpose of evaluating the right-hand integral, then, (K) may be considered a constant, (K)_a. We thus obtain

(4) Hibbert used a 3:1 ratio.

(1) From the Ph.D. Thesis of James R. Wright, June, 1951.

(2) Olin Industries, New Haven, Conn.

(3) H. Hibbert, *J. Chem. Soc.*, **101**, 341 (1912).